## REMARKS

Amended claim 10 has been rewritten in independent form and is otherwise the same claim as canceled claim 14.

Amended claim 18 has been rewritten in independent form and is otherwise the same claim as before being amended.

New claims 23-24 include the feature of "wherein the low dose aspirin is not covalently attached to the COX2 inhibitor", which is an embodiment of the present invention that is inherently included in Paragraph [0010] of Applicants' specification.

The Examiner rejected claims 1, 8, and 16 under 35 U.S.C. §102(a) as allegedly being anticipated by Greenberg *et al.* (Journal of Clinical Pharmacology, 2000, 40 (12, Pt2), pp. 1509-1515).

The Examiner rejected claims 5, 9, and 17 under 35 U.S.C. §103(a) as allegedly being unpatentable over Greenberg *et al.* (The Journal of Clinical Pharmacology, 2000, 40 (12, Pt.2), pp. 1509-1515), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248).

The Examiner rejected claims 1, 5, and 8-22 under 35 U.S.C. §103(a) as allegedly being unpatentable over Lai *et al.* (US 6,306,842 B1) in view of Ares *et al.* (US 5,399,584), and further in view of Shapiro (US 6,444,221) and Drug Facts and Comparison (1995 Edition, pp. 1248).

Applicants respectfully traverse the §102(a) and §103(a) rejections with the following arguments.

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35 U.S.C. §102(a)

The Examiner rejected claims 1, 8, and 16 under 35 U.S.C. §102(a) as allegedly being anticipated by Greenberg *et al.* (Journal of Clinical Pharmacology, 2000, 40 (12, Pt2), pp. 1509-1515).

Since claims 1, 8, and 16 have been canceled, the rejection of claims 1, 8, and 16 under 35 U.S.C. §102(a) is moot.

**35 U.S.C. §103(a): Greenberg n view of Burch and Drug Facts and Comparison**

The Examiner rejected claims 5, 9, and 17 under 35 U.S.C. §103(a) as allegedly being unpatentable over Greenberg *et al.* (The Journal of Clinical Pharmacology, 2000, 40 (12, Pt.2), pp. 1509-1515), and further in view of Burch *et al.* (US 6,552,031) and Drug Facts and Comparison (1995 Edition, pp. 1248).

Since claims 5, 9, and 17 been canceled, the rejection of claims 5, 9, and 17 under 35 U.S.C. §103(a) over Greenberg in view of Burch and Drug Facts and Comparison is moot.

**35 U.S.C. §103(a): Lai in view of Ares and further in view of Shapiro and Drug Facts and Comparison**

The Examiner rejected claims 1, 5 and 8-22 under 35 U.S.C. §103(a) as allegedly being unpatentable over Lai *et al.* (US 6,306,842 B1) in view of Ares *et al.* (US 5,399,584), and further in view of Shapiro (US 6,444,221) and Drug Facts and Comparison (1995 Edition, pp. 1248).

Since claims 1, 5, 8-9, 14, and 16-17 been canceled, the rejection of claims 1, 5, 8-9, 14, and 16-17 under 35 U.S.C. §102(a) over Lai in view of Ares and further in view of Shapiro and Drug Facts and Comparison is moot.

A first reason why claims 10 and 18 are not unpatentable over Lai in view of Ares and further in view of Shapiro and Drug Facts and Comparison is that Lai in view of Ares and further in view of Shapiro and Drug Facts and Comparison does not teach or suggest the feature: "low dose aspirin in the amount of 70-85 mg".

The Examiner argues: "The teaching of Lai differs from the claimed invention in ... use of low dose aspirin. With respect to the claimed low dose aspirin (70-85 mg), those of ordinary skill in the art would have been readily optimized effective dosages as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate dosage for treatment involving each of the above mentioned formulations is routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of Drug Facts and Comparison.

In response, Applicants note that all dosages of aspirin recited in Drug Facts and Comparison for treating an inflammatory disorder are well above the range of 70-85 mg.

Accordingly, the Examiner's argument for modifying Lai for use of aspirin in a range of 70-85 mg is not persuasive.

A second reason why claims 10 and 18 are not unpatentable over Lai in view of Ares and further in view of Shapiro and Drug Facts and Comparison is that Lai in view of Ares and further in view of Shapiro and Drug Facts and Comparison does not teach or suggest the feature: "an antioxidant selected from the group consisting of a flavanoid, a flavonoid, an isoflavone, and combinations thereof".

The Examiner argues: "The teaching of Laid differs from the claimed invention in ... the use of flavonoids, flavanoids or isoflavones in combination with aspirin and COX2 inhibitors.... To incorporate such teaching into the teaching of Lai, would have been obvious in view of Ares who teaches the use of flavonoids or flavones for treating damage to the mucosal lining of gastrointestinal tract caused by NSAID. One having ordinary skill in the art would have motivated to modify the teaching of Lai such that gastrointestinal side effects associated with NSAID such as aspirin (column 1, lines 19-22 of Lai' 842; column 1, lines 14-26 of Ares'584) would be greatly reduced.".

In response, Applicants respectfully contend that the Examiner has not provided any evidence demonstrating that any of rofecoxib, celecoxib, and low dose aspirin cause inflammatory damage, as discussed next.

In response, Applicants respectfully contend that rofecoxib does not cause inflammatory damage. See "Rofecoxib [Vioxx, MK-0966; 4-(4'-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone]: a potent and orally active cyclooxygenase-2 inhibitor. Pharmacological and

biochemical profiles", Chan CC, Boyce S, Brideau C, Charleson S, Cromlish W, Ethier D, Evans J, Ford-Hutchinson AW, Forrest MJ, Gauthier JY, Gordon R, Gresser M, Guay J, Kargman S, Kennedy B, Leblanc Y, Leger S, Mancini J, O'Neill GP, Ouellet M, Patrick D, Percival MD, Perrier H, Prasit P, Rodger I, et al. J Pharmacol Exp Ther. 1999 Aug;290(2):551-60. The abstract of the preceding reference (Chan et al.) is as follows:

> The discoveries that cyclooxygenase (COX)-2 is an inducible form of COX involved in inflammation and that COX-1 is the major isoform responsible for the production of prostaglandins (PGs) in the gastrointestinal tract have provided a rationale for the development of specific COX-2 inhibitors as a new class of anti-inflammatory agents with improved gastrointestinal tolerability. In the present study, the preclinical pharmacological and biochemical profiles of rofecoxib [Vioxx, also known as MK-0966, 4-(4'-methylsulfonylphenyl)-3-phenyl-2-(5H)-furanone], an orally active COX-2 inhibitor, are described. Rofecoxib is a potent inhibitor of the COX-2-dependent production of PGE(2) in human osteosarcoma cells (IC(50) = 26 +/- 10 nM) and Chinese hamster ovary cells expressing human COX-2 (IC(50) = 18 +/- 7 nM) with a 1000-fold selectivity for the inhibition of COX-2 compared with the inhibition of COX-1 activity (IC(50) > 50 microM in U937 cells and IC(50) > 15 microM in Chinese hamster ovary cells expressing human COX-1). Rofecoxib is a time-dependent inhibitor of purified human recombinant COX-2 (IC(50) = 0.34 microM) but caused inhibition of purified human COX-1 in a non-time-dependent manner that could only be observed at a very low substrate concentration (IC(50) = 26 microM at 0.1 microM arachidonic acid concentration). In an in vitro human whole blood assay, rofecoxib selectively inhibited lipopolysaccharide-induced, COX-2-derived PGE(2) synthesis with an IC(50) value of 0.53 +/- 0.02 microM compared with an IC(50) value of 18.8 +/- 0.9 microM for the inhibition of COX-1-derived thromboxane B(2) synthesis after blood coagulation. Using the ratio of the COX-1 IC(50) values over the COX-2 IC(50) values in the human whole blood assay, selectivity ratios for the inhibition of COX-2 of 36, 6.6, 2, 3, and 0.4 were obtained for rofecoxib, celecoxib,

meloxicam, diclofenac, and indomethacin, respectively. In several in vivo rodent models, rofecoxib is a potent inhibitor of carrageenan-induced paw edema (ID(50) = 1.5 mg/kg), carrageenan-induced paw hyperalgesia (ID(50) = 1.0 mg/kg), lipopolysaccharide-induced pyresis (ID(50) = 0.24 mg/kg), and adjuvant-induced arthritis (ID(50) = 0.74 mg/kg/day). Rofecoxib also has a protective effect on adjuvant-induced destruction of cartilage and bone structures in rats. In a (51)Cr excretion assay for detection of gastrointestinal integrity in either rats or squirrel monkeys, rofecoxib has no effect at doses up to 200 mg/kg/day for 5 days. Rofecoxib is a novel COX-2 inhibitor with a biochemical and pharmacological profile clearly distinct from that of current nonsteroidal anti-inflammatory drugs and represents a new therapeutic class of anti-inflammatory agents for the treatment of the symptoms of osteoarthritis and rheumatoid arthritis with improved gastrointestinal tolerability.

In additional response, Applicants contend that celecoxib does not cause inflammatory damage. See "Celecoxib, a selective cyclooxygenase-2 inhibitor for the treatment of rheumatoid arthritis and osteoarthritis", Goldenberg MM. Clin Ther. 1999 Sep;21(9):1497-513. The abstract of the preceding reference (Goldenberg) is as follows:

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs, despite their well-established association with gastroduodenal injury. Recent discovery of the cyclooxygenase (COX) isoenzymes COX-1 and COX-2 has improved our knowledge of the action of NSAIDs. COX-1 is continuously expressed in almost all tissues, where it converts arachidonate to the prostaglandins (PGs) important in homeostatic function; COX-2 is present in immune cells, blood vessel endothelial cells, and synovial fibroblasts. Classic NSAIDs inhibit both COX isoenzymes by occupying the cyclooxygenase-active site, preventing access by arachidonic acid. In theory, a drug such as celecoxib that selectively inhibited COX-2 might block inflammation, pain, and fever while reducing the side effects (gastric erosions and ulcers) associated with inhibition of

COX-1. In animal models of inflammation and pain, celecoxib has shown marked suppression of PG production and inflammation compared with indomethacin, the standard COX-1/COX-2 inhibitor. In clinical trials, celecoxib dosed at 100, 200, and 400 mg BID was found to significantly reduce the signs and symptoms of rheumatoid arthritis (RA) and osteoarthritis. In one RA study, celecoxib was found to be as clinically effective as diclofenac after 24 weeks of treatment; at the end of the study, gastroduodenal ulcers occurred significantly more frequently in the diclofenac group (15%) than in the celecoxib group (4%). In a 1-week endoscopy study comparing celecoxib with naproxen and placebo, the incidence of gastric erosions/ulcers was significantly greater in the naproxen group than in the celecoxib or placebo group. The most common adverse effects of celecoxib in clinical studies were headache, diarrhea, abdominal discomfort, and dizziness. Celecoxib has shown significant equivalent anti-inflammatory and analgesic efficacy and has produced less endoscopically apparent gastrointestinal (GI) ulceration or erosion than have 3 classic NSAIDs. Whether it will have long-term GI adverse effects or interact with other medications to cause serious adverse responses (eg, increased GI bleeding or rash in conjunction with other sulfonamide-like drugs) is unknown and remains to be established.

In additional response, Applicants contend that the Examiner has not cited any reference disclosing that low dose aspirin (70-85 mg) causes inflammatory damage. Although Ares states that aspirin can cause damage to the musocal lining of the gastro-intestinal tract, Ares does not state a minimum aspirin dosage that would cause such damage. There is obviously an aspirin dosage sufficiently small so as to not cause inflammatory damage. The Examiner has not cited any evidence to determine a dividing line between an aspirin dosage that causes inflammatory damage and an aspirin dosage that does not cause inflammatory damage.

Moreover, even if a low dosage of aspirin (70-85 mg) could cause such damage to the mucosal lining of the gastro-intestinal tract, it is not obvious to add the claimed flavanoid or flavonoid to the composition of low dose aspirin and COX2 inhibitor to treat or prevent such damage, because maximum therapeutic benefit would be achieved if aspirin-COX2 inhibitor and flavanoid/flavonoid are independently administered to the subject at their respective optimal frequency, rather than being administered in the same composition.

Ares, col. 6, lines 40-45 recites: "The frequency of administering the above amounts of Compound is preferably from about every other day to about four times daily, more preferably from about once daily to about thrice daily, more preferably still from about once daily to about twice daily."

Ares, col. 6, lines 6-14 recites: "The safe and effective amount of a material will vary with the particular condition being treated, the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the specific composition employed, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician."

Applicants maintain that the preceding quotes from Ares indicates that the relationship of the flavanoid/flavonoid to the concurrent therapy (using aspirin - COX2 inhibitor) and the frequency of administration of the flavanoid/flavonoid is highly variable, which suggests that constraining the frequency of administration of the flavanoid/flavonoid to be the same frequency of administration of the aspirin - COX2 inhibitor (as is the case if the flavanoid/flavonoid is in the same composition as the aspirin - COX2 inhibitor) would severely limit the ability to optimize the use of the flavanoid/flavonoid. Therefore, it is obvious to administer the

flavanoid/flavonoid independent of the aspirin - COX2 inhibitor composition, and it is accordingly not obvious to include the flavanoid/flavonoid within the aspirin - COX2 inhibitor composition, so that the frequency of administration of the flavanoid/flavonoid could be optimized instead of being constrained.

The Examiner additionally argues: "Shapiro (US 6444221) teaches the use of flavonoids, flavanoids and isoflavones (i.e., daidzin, genistein, quercetin, silymarin, etc...) as antioxidants having functional equivalent property for the treatment of inflammatory disease conditions (column 9, line 52 thru column 19, line 32; column 20, line 47 thru column 21, line 8).... Shapiro is being supplied as a reference to demonstrate the use of flavonoids, flavanoids and isoflavones as antioxidants that are useful in the treatment of inflammatory disease conditions.

In response, Applicants contend that Shapiro teaches that the disclosed flavonoids, flavanoids and isoflavones as antioxidants are useful in treating of inflammatory disease only in combination with carbonyl trapping agents. See Shapiro, col, 10, lines 43-51. See also, Shapiro, col, 10, lines 59-67 ("In another preferred embodiment, use of a primary agent in combination with a clinically effective anti-oxidant and lipid peroxidation inhibitor co-agent may be of particular benefit in preventing or ameliorating forms of chronic inflammation by incorporating two pharmacological strategies, the sequestering of cytotoxic aldehydes and ketones generated at sites of chronic inflammation and the sequestering of activated oxygen chemical species generated earlier in the non-enzymatic inflammatory cascade.").

Therefore, Applicants respectfully contend that Shapiro does not teach that the disclosed flavonoids, flavanoids and isoflavones as antioxidants are useful in treating of inflammatory

disease in combination with low dose aspirin and COX2 inhibitor. Accordingly, it would not be obvious to add the disclosed flavonoids, flavanoids and isoflavones as antioxidants to Lai's composition of aspirin and COX2 inhibitor for the purpose of treating of inflammatory disease.

Based on the preceding arguments, Applicants respectfully maintain that claims 10 and 18 are not unpatentable over Lai in view of Ares and further in view of Shapiro , and that claims 10 and 18 are in condition for allowance. Since claims 11-13 and 15 depend from claim 10, Applicants contend that claims 10-13 and 15 are likewise in condition for allowance. Since claims 19-22 depend from claim 18, Applicants contend that claims 19-22 are likewise in condition for allowance.

In addition with respect to claims 11, 13, 19, and 21, Lai in view of Ares and further in view of Shapiro does not teach or suggest the feature: "wherein the antioxidant comprises the flavanoid" (claims 11 and 19) and "wherein the antioxidant comprises the isoflavone" (claims 13 and 21).

Ares is silent regarding flavanoids and isoflavones. Moreover, Shapiro does not teach that flavanoids and isoflavones as antioxidants are useful in treating of inflammatory disease in combination with low dose aspirin and COX2 inhibitor, as discussed *supra*. Accordingly, Applicants respectfully contend that the Examiner has not established a *prima facie* case of obviousness in relation to claims 11, 13, 19, and 21.

In addition with respect to claims 15 and 22, Lai in view of Ares and further in view of

Shapiro does not teach or suggest the feature: "wherein the therapeutic composition is in an enteric coated formulation". Applicants note that the Examiner did not provide any argument to support the rejection of claims 15 and 22. Accordingly, Applicants respectfully contend that the Examiner has not established a *prima facie* case of obviousness in relation to claims 15 and 22.

## CONCLUSION

Based on the preceding arguments, Applicants respectfully believe that all pending claims and the entire application meet the acceptance criteria for allowance and therefore request favorable action. If the Examiner believes that anything further would be helpful to place the application in better condition for allowance, Applicants invites the Examiner to contact Applicants' representative at the telephone number listed below. The Director is hereby authorized to charge and/or credit Deposit Account No. 19-0513.

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